

# Skin Changes in the Elderly People – How Strong is the Influence of the UV Radiation on Skin Aging?

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## ABSTRACT

*Just like every other part of the organism, the skin ages as a result of the passage of time. That process is called chronologic or intrinsic aging. However, skin is also exposed to external insults, such as UV radiation, which is the most influential extrinsic factor in skin aging, causing so called photoaging or extrinsic skin aging. Photoaging is a cumulative process which depends on the degree of UV exposure and the skin type. It is much more visible in individuals with skin types I and II and, less prominent in dark-skinned population. Chronic sun exposure can result in numerous changes in human skin, particularly on the face, nape, and arms. Keratinocytes, melanocytes, fibroblasts, and endothelial cells are altered by UV radiation. Therefore, changes in photoaging include wrinkling, elastosis, actinic keratoses, irregular pigmentation, telangiectases, and the development of malignant skin tumours. In the last decades, important progress has been made in understanding molecular mechanisms of photoaging. It is a complex process in which UV radiation has effects on numerous molecular processes that damage the skin, especially connective tissue of the skin. These processes include cell surface receptors, certain signal transduction pathways, transcription factors and, various enzymes involved in the synthesis and degradation of the dermal elements. Initial process in the activation of this process is UV-induced generation of the reactive oxygen species, which can also directly damage cell's DNA, membrane and proteins. Most of alterations found on the photoaged skin had formerly been considered to be caused by UVB wavelengths. However, a number of recent studies have demonstrated that UVA can also cause burning, elastosis, and skin cancer.*

**Key words:** aging, skin aging, photoaging, UV radiation, elderly population

## Introduction

In the last centuries, human lifespan has increased, especially in developed countries. For example, the life expectancy in Sweden for women today is 82 years and 77 years for men<sup>1</sup>. With a share of people than 65 years of 16.64% in total population, Croatia is considered to be a very old country regarding its population. Demographic projections reveal a further increase in the share of people over 65 years in future<sup>2</sup>. Today's lifestyle has resulted in increased sun exposure throughout the whole lifetime. Therefore, with the rise in the share of elderly population, there is an increase in the part of population with significantly photodamaged skin. Increased cosmetic consciousness and longer human lifespan resulted in the

fact that in recent years greater attention has been given to the accelerated signs of aging skin with the emphasis on the role of the UV radiation. The signs of accelerated skin photodamage or photoaging include a wide spectrum of benign, premalignant and malignant skin lesions. Benign skin changes in photoaged skin are hyper and hypopigmentations, decreased elasticity, fine and coarse wrinkles, solar comedones and keratoses. Serious lesions that are commonly found on chronically sun-exposed skin are actinic keratoses and lentigo maligna. The most deleterious effect of UV radiation is the development of various types of skin malignancies such as basal cell carcinoma, squamous cell carcinoma and melanoma.

## Aging theories

The process of aging is one of the most complex and fascinating biological phenomena. Aging is a genetically regulated process in which the organism's maximum life-span potential is pre-determined and, the rate of aging is influenced by environmental factors and lifestyle. Considering the complexity of mechanisms involved in the regulation of aging process, up to this date there isn't a major, unifying theory which could explain them<sup>3</sup>. Aging could be defined as a progressive loss of function accompanied by increase in frailty, morbidity and mortality with advancing age<sup>1</sup>. Most of the data indicate that aging is characterized by a stochastic accumulation of molecular damage and a progressive failure of maintenance and repair, and the genes involved in homeodynamic pathways are the most likely candidate virtual gerontogenes<sup>4</sup>. Today, several groups of gerontogenes are identified in organisms such as yeasts, nematodes, fruit flies and mice. There are gerontogenes involved in the stress response alterations, including DNA repair genes, tumour suppressor genes (like p53), the genes encoding antioxidative enzymes. Another group of gerontogenes is involved in the energy management, encoding the enzymes important for the ATP synthesis, regulators of insulin and growth hormone. The third group of gerontogenes are those controlling the cell division and, the main members of this group are telomerases, which repair telomere loss<sup>1</sup>. Telomeres are the protective terminal portions of eukaryotic chromosomes consisting of hundreds of tandem short sequence repeats that lack the genetic information and are reduced in length during each replication<sup>1,5</sup>. Critically short telomeres induce proliferative senescence or apoptosis, depending on the cell type, and appear to compromise DNA stability and transcription of subtelomeric genes, presumably contributing to the aged phenotype<sup>6</sup>. Therefore, telomeres act as molecular clocks.

## Skin Aging

Just like every other part of the organism, the skin ages due to the passage of time. This process is called chronologic or intrinsic aging. However, skin is also exposed to external insults, such as UV radiation, which is the most influential extrinsic factor in skin aging. It causes photoaging or extrinsic skin aging (dermatoheliosis). Aging due to chronic sun exposure (photoaging) is characterized clinically by wrinkling, dyspigmentation and many other changes<sup>7</sup>. Chronologic and photoaging of skin have been distinguished at the structural, cellular and molecular levels<sup>8</sup>.

## Functional and Histological Features of the Photoaged Skin

The structure of the skin is complex, and every part of it is affected by the process of aging, including epidermis, dermis, extracellular matrix, vascular and adnexal structures. The changes of the aging skin are reflected in both morphological and functional aspects. Functional distur-

bances include: reduced DNA repair; reduced immune response, aberrant epidermal water balance, diminished sweat and sebum production, impaired temperature control, reduced vascular reactivity in intrinsic aging (although some enhancement of vascularity in photoaging can be observed, such as telangiectases), slowed vitamin D metabolism, decreased resistance to pressure, impaired wound healing and reduced cell proliferation<sup>1</sup>.

Histologically, epidermal changes include thinning of stratum spinosum with flattening of the dermo-epidermal junction and disappearing of the zipper-like communication between the rete ridges and the dermal papillae. Clinically, it can be seen as the fragility of skin in the elderly people, with the tendency of blisters formation in response to relatively weak shearing forces<sup>1</sup>. The keratinocytes increase in size and become more irregular, especially in photodamaged areas of the skin, however, they are generally fewer in number. The senescent keratinocytes become resistant to apoptosis and may survive for a long time, giving time for DNA and protein damage to accumulate with possible implication for carcinogenesis. The number of melanocytes decreases with age. Dysregulation of melanocyte density results in the development of various pigmentary skin changes, including freckles, guttate hypo-melanosis, lentigines and nevi. The number of dendritic Langerhans cells also decreases with age, the cells get less dendrites and have reduced antigen-trapping capacity<sup>9</sup>. Major changes in the skin photoaging process are those involving the structure of dermal connective tissue. In aging skin dermis becomes thinner and relatively acellular. There are fewer collagen fibres, altered elastic fibres, and reduced extracellular matrix. Photoaged skin is characterised by accumulation of disorganised elastin and its microfibrillar component fibrillin in the deep dermis, and by severe loss of interstitial collagens, the major structural proteins of the dermal connective tissue<sup>10</sup>. Type I collagen, which accounts for 80% of dermal structural proteins becomes significantly reduced, as well as fibrillin-1. On the other hand, the production of disorganised and non-functional elastin and tropoelastin becomes significantly increased. The deposition of these dystrophic elastic fibres in the dermis is a prominent histological feature in photoaged skin. This process is called solar elastosis<sup>1</sup>.

In aged skin, the function of sweat and sebaceous glands is decreased, however, the volume of the sebaceous glands is increased. Hair and nail growth is slower, nails become fragile, while hair is reduced in number and changed in structure (depigmented and finer, velus hairs). Subcutaneous fat is also reduced<sup>1</sup>.

## Clinical Features of Photoaged Skin

Photoaging is more common and much more visible in people with skin types I and II, and less prominent in dark-skinned population. Individuals with outdoor lifestyles, people who live in sunny geographical areas, and fair-skinned people will experience the greatest degree of photoaging. Areas of chronic sun exposure, such as the face, nape, and arms, are most severely affected. Intrin-

sically aged skin is dry and pale, wrinkles are fine and there is marked decrease in elasticity. On the other hand, signs of photoaged skin include fine and severe wrinkling with deep furrows, hyper and hypopigmentations, telangiectases, atrophy and various premalignant and malignant skin lesions. The role of the UV radiation in the development of seborrheic keratoses is unclear, however, there are authors who believe that sunlight plays an important role in their development<sup>1</sup>. Seborrheic keratoses are usually called »old age spots« or »solar lentigines«. The most common sites of the flat, tan-pigmented form of seborrheic keratoses are the dorsal sides of the hands and face, however, in elderly population these lesions can be seen on the trunk, too. Keratinocytes, melanocytes, fibroblasts, and endothelial cells are all altered by UV radiation. Damaged keratinocytes lead to the development of actinic keratoses which histologically represent squamous cell carcinoma in situ with the potential to further evolve into invasive form. Damage to melanocytes may produce hyper and hypopigmentations, and also the development of malignant lesions such as lentigo maligna and lentigo maligna melanoma. Favre-Racouchot disease (nodular elastosis with cysts and comedones) typically develops in older men, beginning with the development of comedones and numerous small cysts and yellow aspect of the skin, due to solar elastosis. Usual site of skin lesions are lateral aspects of cheeks, periorbital regions, temples and nose. Cutis rhomboidalis nuchae or »sailor's/farmer's neck« clinically presents with deep furrows in a rhomboid pattern on the nape, associated with thickened skin and yellow plaques. Erythrosis interfollicularis colli (erythromelanosus interfollicularis colli) is another common form of UV-damaged skin with sharply demarcated erythema, usually on the neck, with the perifollicular pale areas.

### *The Molecular Mechanisms of UV Radiation in Photoaging*

In the last decades, substantial progress has been made in understanding cellular and molecular mechanisms of chronological aging and photoaging. It has been shown that chronological aging and photoaging share fundamental molecular pathways<sup>11</sup>. Accelerated skin aging caused by UV radiation is a complex process in which UV radiation influences numerous molecular processes affecting every unit of the skin, with the greatest impact on the connective tissue of the skin. The principle pathogenic mechanism is the accumulation of damage through the oxidative stress<sup>1</sup>. The formation of reactive oxygen species and the induction of metalloproteinases reflect central aspects of skin aging<sup>12,13</sup>. Initial step is UV-induced generation of the reactive oxygen species (ROS) such as superoxide anion, peroxide and singlet oxygen<sup>11</sup>, which can also directly damage cell's DNA, membrane and proteins. Immediately after the UVA or UVB exposure, there is both, direct photochemical accumulation of ROS and activation of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which then generates hydrogen peroxide. That way, the synthesis of ROS

is amplified since hydrogen peroxide can be converted to other ROS, such as hydroxyl radical and singlet oxygen<sup>11</sup>. It has been shown that the level of hydrogen peroxide in human skin increases within 15 minutes following the UV exposure and continues to accumulate for approximately 60 min after exposure. In contrast to hydrogen peroxide generation, direct generation of ROS occurs only during UV exposure and abates after the UV exposure<sup>11</sup>.

UV radiation causes activation of the cell surface receptors for cytokines (interleukin 1 and tumour necrosis factor alpha, IL-1 and TNF $\alpha$ ) and growth factors such as epidermal growth factor (EGF) on keratinocytes and fibroblasts<sup>11</sup>. Activated cell surface receptors stimulate signal transduction cascades which induce transcription factor AP-1 resulting in transcription of matrix metalloproteinase genes (matrix metalloproteinase 1, 3 and 9; MMP-1, MMP-3 and MMP-9). Additionally, AP-1 in fibroblasts inhibits procollagen gene expression by binding and sequestering factors which are part of a transcription complex necessary for procollagen synthesis. Matrix metalloproteinases which are secreted from keratinocytes and fibroblasts break down collagen and other dermal proteins. Once cleaved by MMP-1, collagen can be further degraded by MMP-3 and MMP-9<sup>11,14</sup>. Inability to repair all of dermal damage affects functional and morphological integrity of the extracellular matrix. These processes result in a drastic change in homeostasis of dermal connective tissue with the development of the previously described solar elastosis. It has been shown that mitochondria are also involved in photoaging. At the molecular level, photoaged skin is characterized by increased amounts of large-scale deletions of the mitochondrial genome. The common deletion can be generated in dermal fibroblasts through repetitive UVA irradiation, and this was found to be associated with an increased expression of the collagen-degrading enzyme MMP-1<sup>15</sup>. In the recent study by Amano S. et al<sup>16</sup>, internal changes of sun-exposed skin were compared with those of sun-protected skin. Their results suggest that the basement membrane at the dermal-epidermal junction of sun-exposed skin becomes damaged and multilayered and partly disrupted compared with that of sun-protected skin. Basement membrane plays important roles in maintaining a healthy epidermis and dermis, and repeated damage destabilizes the skin, accelerating the aging process. They found that matrix metalloproteinases (MMPs) and urinary plasminogen activator are increased in UV-irradiated skin. MMPs were detected in the cornified layer in sun-exposed skin, but not in sun-protected skin. Using skin-equivalent models, they found that MMPs and plasmin cause damage of the basement membrane and that its reconstruction is enhanced by inhibiting these proteinases, as well as by increasing the synthesis of the basement membrane components. Therefore, the enhancement of the basement membrane repair mechanisms might be a useful strategy to postpone the process of photoaging<sup>16</sup>.

## Photocarcinogenesis

The carcinogenicity (photocarcinogenicity) of UV rays from sunlight to human skin has been recognized more than a century ago<sup>17</sup>. UV radiation can damage DNA, causing gene mutations and, leading to the development of malignant tumours such as basal cell carcinoma, squamous cell carcinoma and melanoma.

UVB primarily affects the epidermis causing disruption in DNA and the formation of pyrimidine dimers which leads to modifications in oncogene and tumour suppressor gene expression, the most important event in tumour initiation. In addition, UVB effects the production of ROS (e.g. hydrogen peroxide, superoxide anions and singlet oxygens). These induce single strand breaks in DNA<sup>18</sup>. Besides causing mutations in the critical regulatory genes of DNA of keratinocytes, UV radiation also diminishes the immune response in the skin. UV radiation may promote cancer through indirect mechanisms, e.g. immunosuppression and dysregulation of growth factors. The carcinogenic process probably involves multiple sequential steps, some, but not all of which involve alterations in DNA structure<sup>19</sup>.

## Prevention and Therapy

Nowadays there are many options in the treatment of changes caused by photoaging. These methods are usually applied to ameliorate cutaneous signs of aging in general. Some improvement of photoaging may be achieved with the well advised use of topical retinoic acid (tretinoin) and, possibly with alpha hydroxy acids. Retinoids, either naturally occurring or synthetic, are defined by their ability to bind nuclear retinoid receptors of the steroid/thyroid superfamily. Their key function in physiology is control of cellular proliferation and differentiation. Topical retinoids, namely tretinoin, have been proven to prevent and repair clinical features of photo-

aging; these processes are facilitated by an ability to prevent loss of collagen (inhibition of collagenase synthesis) from dermis, and stimulate new collagen formation in the papillary dermis of sun-exposed skin<sup>20,21</sup>. There has been an increased interest in the use of natural antioxidants such as vitamins to help restore dermal antioxidant activity. Products containing alpha-tocopherol (vitamin E), L-ascorbic acid (vitamin C), retinol (vitamin A), and niacinamide (vitamin B3), are considered to be effective in the treatment of photoaging<sup>22</sup>. Chemical peels, dermabrasion and plastic surgery can also reduce or eliminate certain signs of photodamaged skin. However, the most effective measure of prevention of the photo-aging and photocarcinogenesis is sun protection. In this context skin protection in children is of particular importance since children usually spend a lot of time outdoors and cannot provide themselves with sun protection measures as adults can. In addition to this, sunburn reactions in childhood are shown to be particularly important in the development of melanoma<sup>23–26</sup>.

## Conclusion

Chronological or intrinsic skin aging is an inevitable process which is a result of the passage of time. However, photoaging or extrinsic aging of the skin is a complex, cumulative process caused by the chronic exposition to UV radiation. The influence of UV radiation on the development of both, cosmetic and serious and, potentially even life-threatening skin lesions in elderly population is undeniably strong. The key role of extrinsic factors in skin aging and the detection of its mechanisms has given rise to development of various therapeutic and preventive strategies. However, the most important factor in the prevention of both, photoaging and photocarcinogenesis remains the sun protection.

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## **PROMJENE NA KOŽI U OSOBA TREĆE DOBI – KOLIKI JE UTJECAJ UV ZRAČENJA NA STARENJE KOŽE?**

### **S A Ž E T A K**

Kao i svaki djelić ljudskog organizma, koža podliježe starenju koje je rezultat prolaska vremena, a taj se proces naziva kronološkim ili intrinzičkim starenjem. No, koža je također izložena vanjskim čimbenicima, kao što je UV zračenje. UV zračenje je najutjecajniiji vanjski čimbenik koji utječe na starenje kože uzrokujući tzv. fotostarenje ili ekstrinzičko starenje kože. Fotostarenje kože je kumulativni proces koji ovisi o količini izloženosti UV zračenju, kao i o tipu kože. Fotostarenje je osobito izraženo u osoba s kožom tip I i II u odnosu na osobe tamne puti. Kao posljedica kronične izloženosti suncu, na koži se u starijih osoba mogu vidjeti brojne promjene, poglavito u području lica, zatiljka i ruku. UV zračenje negativno djeluje na keratinocyte, melanocyte, fibroblaste i endotelne stanice. Stoga se u kliničkoj slici mogu vidjeti promjene poput bora, elastoze, nepravilnih pigmentacija, teleangiectazija, aktiničkih keratoza i drugih, dobroćudnih, ali i zloćudnih tumora kože. Posljednjih desetljeća postignut je znatan pomak u razumijevanju molekularnih mehanizama fotostarenja. To je vrlo složen process u kojem UV zračenje ima brojne učinke na kožu, a osobito na vezivno tkivo dermisa. Dolazi do aktivacije površinskih staničnih receptora, aktivacije određenih signalnih transdukcijskih mehanizama te različitih enzima važnih za sintezu i razgradnju dermalnih elemenata. Inicijalni korak u tom procesu je UV zrakama inducirano nakupljanje reaktivnih kisikovih radikala, koji mogu i izravno oštetiti staničnu DNA, membranu i proteine u stanici. Do nedavno je bio uvriježen stav da su navedene promjene rezultat djelovanja isključivo UVB zraka. No, posljednjih godina istraživanja su pokazala da i UVA zrake imaju ulogu u nastanku opekline, solarne elastoze i karcinoma kože.